

REVIEW ARTICLE

Role of microRNAs in inflammatory upper airway diseases

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Abstract

MicroRNAs (miRNAs) are a conserved family of small endogenous noncoding RNA molecules that modulate post-transcriptional gene expression in physiological and pathological processes. miRNAs can silence target mRNAs through degradation or inhibition of translation, showing their pivotal role in the pathogenesis of many human diseases. miRNAs play a role in regulating immune functions and inflammation and are implicated in controlling the development and activation of T and B cells. Inflammatory chronic upper airway diseases, such as rhinitis and rhinosinusitis, are spread all over the world and characterized by an exaggerated inflammation involving a complex interaction between immune and resident cells. Until now and despite allergy, little is known about their etiology and the processes implicated in the immune response and tuning inflammation of these diseases. This review highlights the knowledge of the current literature about miRNAs in inflammatory chronic upper airways diseases and how this may be exploited in the development of new clinical and therapeutic strategies.

KEYWORDS

allergic rhinitis, chronic rhino sinusitis, miRNAs, nasal polyps, non-allergic rhinitis

1 | INTRODUCTION

MicroRNAs (miRNAs) are a conserved family of small RNA molecules (18–22 nucleotides in length) that regulate post-transcriptional gene expression. Their mechanism of action induces either translational repression or mRNA degradation.¹

The discovery of the first miRNA, lin-4, in 1993 by Lee et al² in the nematode *Caenorhabditis elegans*, revolutionized the field

of molecular biology. Since then, over 1,000 human miRNAs have been discovered and detected in all animal model systems; however, the biological function of the majority of them is still unknown.

MicroRNAs have been described to be involved in many biological processes such as proliferation, apoptosis, differentiation, and survival.^{3–6} Recent studies indicated the regulatory role of miRNAs in developmental processes. Boyer et al. performed miRNA

Abbreviations: 4E-T, eIF4E transporter; ACOPD, Asthma Chronic Obstructive Pulmonary Disease; Ago, Argonaute proteins; ALI, Air-Liquid Interface; AR, Allergic Rhinitis; AR-A, AR-Asthma; CB, Cord Blood; CRS, Chronic Rhinosinusitis; CRSsNP, CRS without nasal polyps; CRSwNP, CRS with nasal polyps; DGCR8, DiGeorge Syndrome critical region 8; EPO5, Exportin 5; ES, Embryonic Stem; EVs, Extracellular Vesicles; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; HBECs, Human Brain Microvascular Endothelial Cells; HSC, Hematopoietic Stem Cells; IFN, Interferon; IRIS, Immune Reconstitution Syndrome; KEGG, Kyoto Encyclopedia of Genes and Genomes; MAPK, Mitogen-Activated Protein Kinase; MCs, Mast cells; miR, microRNA; NANOG, Nanog Homeobox; NAR, Non-Allergic Rhinitis; Nucleotides, nt; OPN, Osteopontin; OVA, Serum Ovalbumin; PABPC, Poly(A)-Binding Protein; PBMC, Peripheral Blood Mononuclear Cells; POU5F1, POU Class 5 Homeobox 1; pRB, Phosphorylated Retinoblastoma Protein; Pri-miRNA, Primary miRNA; PTEN, Phosphatase and Tensin Homolog; RISC, RNA-Induced Silencing Complex; SCIT, Subcutaneous immunotherapy; SIT, Specific Immunotherapy; SLIT, Sublingual Immunotherapy; SOX2, Sex-Determining Region Y(SRY)-Box 2; SPT, Skin Prick Test; TB, Tuberculosis; TGFBR2, Transforming Growth Factor-Beta Receptor 2; Th, T Helper; TNF α , Tumor Necrosis Factor-Alpha; UAD, United Airway Diseases; UTR, Un-translated Region; VD3, Vitamin D3.

expression analyses in human embryonic stem (ES) cells. They found that developmental transcription factors POU class 5 homeobox 1 (POU5F1), sex-determining region Y (SRY)-box 2 (SOX2), and Nanog Homeobox (NANOG) interacted with 14 miRNAs in an ES cell line. Moreover, these transcription factors bonded the promoters of miR-137 and miR-301 genes.⁷ As well as hematopoietic stem cells (HSC) go through proliferation, commitment, maturation, and apoptosis. In these processes, three miRNAs miR223, miR-181, and miR-142 are preferentially involved and expressed in hematopoietic tissues.⁸ Also during the development of skeletal and cardiac muscles, miR-1 and miR-133 have been described to co-regulate events in a variety of organisms.⁹ Thus, a characteristic miRNA expression signature is crucial in the different stages of embryonal and tissue development. Any abnormal miRNA expression may represent defects in the spatial and temporal regulation which finally could be lethal. Besides, miRNAs regulate the different steps of the cell cycle in both a positive and negative manner. Some of them, like miR-15a-16-1 cluster, are known to cause cell cycle arrest by inhibiting cell cycle regulators, such as CDK1, CDK2, CDK6, and cyclins.¹⁰ On the other hand, some miRNAs induce proliferation by targeting key regulators of CDK4/pRB (phosphorylated retinoblastoma protein) pathway.¹¹ Moreover, miRNAs also contribute to the regulation of the different signaling pathways. For instance, several miRNAs such as miR-21, miR-26a, miR-221, and miR-222 target the Phosphatase and tensin homolog (PTEN) which is a signaling molecule in the PI3K pathway promoting cell survival.¹² Finally, it worth to be noted that miRNAs are also implicated in the immune response.^{13–15} In the case of the innate immune system, the expression profiling of 200 microRNAs in human monocytes revealed that several of them (miR-146a/b, miR-132, and miR-155) regulate immune responses after pathogen recognition.¹⁶ miR-146 induction may occur only in response to IL-1 and tumor necrosis factor (TNF) or bacterial stimuli, whereas the overexpression of miR-155 is induced by pro-inflammatory cytokines after both bacterial and viral exposure.¹⁷ On the other hand, in the adaptive immune system response, miR-21, miR-22, miR-24, miR-103, miR-155, and miR-204 are up-regulated in T-cell activation, while miR-16, miR-26, miR-30, miR-150, and miR-181 are suppressed.¹⁸ Conclusively, it is obvious that the deregulated expression of miRNAs has been associated with several human diseases, ranging from metabolic and malignancy to autoimmune or inflammatory.^{19–22}

Inflammatory upper airway diseases are spread all over the world and with high prevalence.^{23,24} Rhinosinusitis is an inflammatory disease of the nasal cavities and paranasal sinuses characterized by a set of symptoms (nasal congestion, anterior rhinorrhea or post-nasal drip, reduction/loss of smell, and facial pain pressure) which persists during at least 12 consecutive weeks in the case of Chronic Rhinosinusitis (CRS) with two main presenting phenotypes, with (CRS_{NP}) and without (CRS_{NP}) nasal polyps.^{25–29} Rhinitis also affects the nasal cavities and is characterized by nasal symptoms (nasal congestion, rhinorrhea, nasal itching, sneezing, and even loss of smell in severe cases).³⁰ Depending on the primary cause, rhinitis can be classified as Allergic (AR) or non-allergic (NAR). Moreover, in the last 10–15 years, the evidence showing the link between

upper and lower airways has been investigated under the concept of United Airway Diseases (UAD).³¹ The relationship between the nose and lung inflammation mechanisms has been highlighted by epidemiological investigations^{32,33} and clinical trials.³⁴ Recent cross-sectional studies underline that AR and asthma commonly occur together and share the same genetic background. Moreover, it seems that upper airway symptoms either precede or start at the same time as asthma.^{35–37} Thus, AR is commonly associated with “early-onset asthma,” which is reported to have an onset before 16 years of age. Conversely, CRS is associated with “late-onset asthma,” which is reported to have started at or after the age of 16.^{38–43} Exaggerated inflammation is the hallmark of these diseases which involve a complex regulation mechanism between immune and resident cells,⁴⁴ and their etiology remains unclear. In clinical medicine, the observable characteristics or “traits” associated with a disease are termed “phenotype.” The different phenotypes associated with CRS and AR may also have different pathophysiological mechanisms or so-called “endotypes.” Thus, endotyping of these diseases would help in a better understanding of the mechanisms involved in tuning immune response and inflammation. Finally, it would be essential to develop adequate treatments, from pharmacotherapy to surgery and biologics.^{45–49}

Recently, the role of miRNAs in CRS and AR has been investigated with growing interest.⁵⁰ In this review, we summarize the latest knowledge about the role and function of miRNAs to underline their potential usage as biomarkers for the diagnosis, and as targets for the treatment of CRS and AR.

2 | miRNA BIOGENESIS AND REGULATION

miRNA biogenesis is a multistep process. It begins in the nucleus, where the RNA polymerase II transcribes the miRNA genes localized in the intron or noncoding protein regions into long primary miRNA (pri-miRNAs) transcripts (generally >1 kb). The pri-miRNAs undergo an endonucleolytic cleavage by the Microprocessor Complex, comprising the RNase II Enzyme Drosha and the protein DiGeorge Syndrome Critical Region 8 (DGCR8).⁵¹ Drosha recognizes the double-strand-RNA-single strand RNA junction at the hairpin base, whereas DGCR8 proteins bind the stem to ensure a correct cleavage (Figure 1). The resulting 70-nucleotides (nt) pre-miRNA is actively transported into the cytoplasm by Exportin 5 (EPO5)-Ran-GTP Complex. In the cytoplasm, the RNase III Enzyme Dicer cleaves the pre-miRNAs at a species-specific length leading to a 22-nt-double-stranded miRNA. One strand of this Complex, the “guide strand,” represents the mature miRNA which is incorporated into the RNA-induced silencing complex (RISC), while the other strand, the “passenger strand,” is discarded. Assembled into the RISC, the miRNA regulates gene expression by base pairing of the 5' end of mature miRNAs (the seed sequence) to the 3' untranslated region (3'UTR) of the target mRNAs (Figure 1). If the complementarity level is complete, and if the miRNA is associated

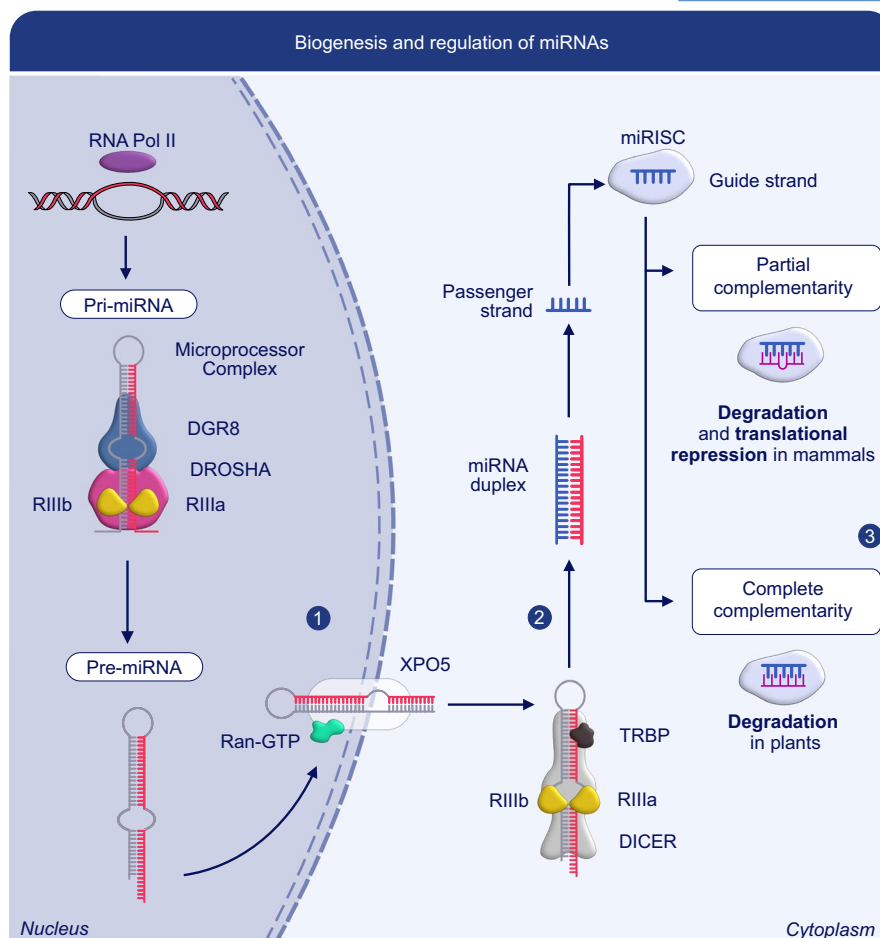


FIGURE 1 Biogenesis and regulation of microRNAs. 1) In the cell nucleus, RNA polymerase II transcribes the miRNA genes into primary miRNA (pri-miRNAs) transcripts (generally >1 kb). Then, Microprocessor Complex comprising the RNase II Enzyme Drosha and the protein DiGeorge Syndrome Critical Region 8 (DGR8) cleaves the pri-miRNA into the 70-nucleotides (nt) pre-miRNA which is transported into the cytoplasm by the Exportin 5 (EPO5)-Ran-GTP Complex. 2) In the cytoplasm, the RNase III Enzyme Dicer cleaves the pre-miRNAs leading to a 22-nt-double-stranded miRNA. One strand of this Complex, the "guide strand," represents the mature miRNA which is incorporated into the RNA-induced silencing complex (RISC), while the other strand, the "passenger strand," is discarded. 3) Assembled into the RISC, the miRNA regulates gene expression by base pairing of the 5' end of mature miRNAs (the seed sequence) to the 3' un-translated region (3'UTR) of the target mRNAs. This interaction can lead to target mRNA degradation or translational repression

with Argonaute proteins (Ago) catalyzing the endonucleolytic reaction, the miRNA directs the cleavage of the target transcript. This pathway is more common for plant miRNAs and represents also the basis of mRNA-knockdown using the siRNAs technologies into mammalian cells (Figure 2). Otherwise, if the complementarity is partial, Ago recruit the adaptor protein TNRC6, which interacts with the poly(A)-binding protein (PABPC) associated with the mRNA poly(A) tail and also recruits deadenylase complexes (such as the PAN2-PAN3 and the CCR4-NOT complexes). The deadenylases' cut of the poly(A) tail causes the mRNA destabilization through decapping and 5'-to-3' exonucleolytic decay. The TNRC6 recruitment leads not only to the mRNA degradation but also to the mRNA less efficiently translated. The CCR4-NOT complex recruits the DDX6, a helicase that binds the decapping complex and inhibits translation. Besides, DDX6 interacts with eIF4E transporter (4E-T), which competes with eIF4G for binding to eIF4E and promotes both the decay and translational repression

of target mRNA. This pathway is more common for mammals, including humans (Figure 2).⁵²⁻⁵⁴ Notably, there is evidence of the emerging role of miRNAs as positive regulators of gene expression as they can stabilize the target mRNAs or induce the transcription process by binding the promoter regions.⁵⁵ The fine-tune gene expression regulation of miRNAs in eukaryotic cells is orchestrated by the principals of multiplicity, cooperativity, and redundancy. According to the "multiplicity," a single miRNA can target various effector genes of a particular pathway. On the other hand, individual mRNAs can be regulated by different miRNAs in parallel as most mRNAs possess multiple binding sites for miRNAs, which is known as "cooperativity". Finally, many miRNAs regulate several cellular processes by targeting various effector genes of different pathways, thereby ensuring cellular homeostasis. This phenomenon is called "redundancy."^{56,57}

Different computational algorithms are used to predict miRNA-mRNA interactions. The principal step of the bioinformatics

The dominant mechanisms of miRNAs in animals

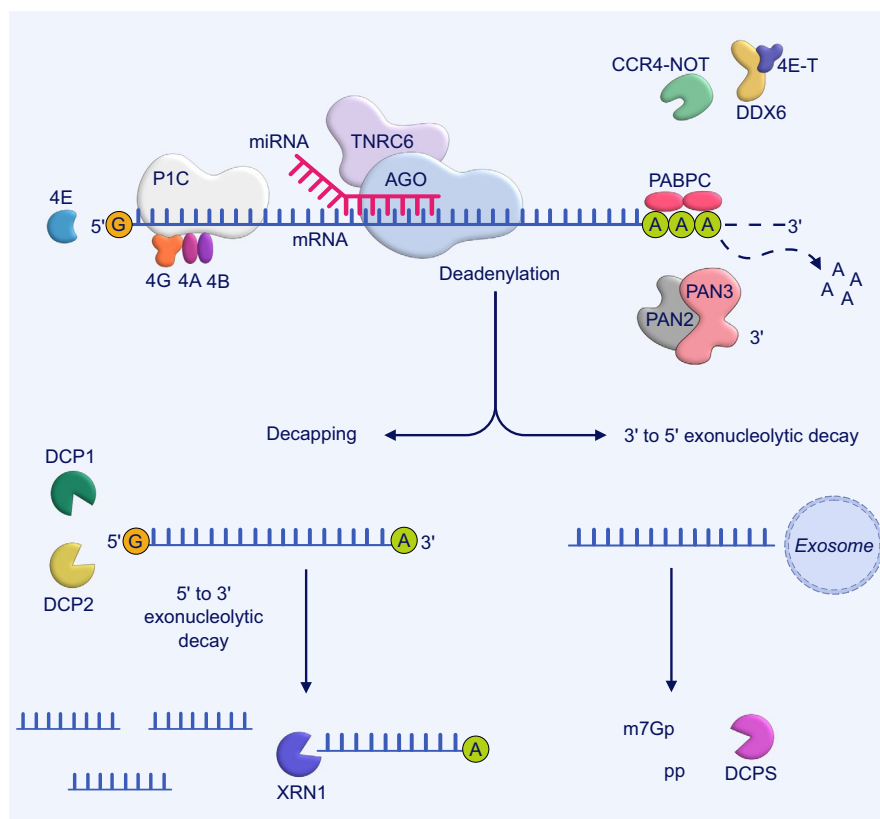


FIGURE 2 The dominant Mechanisms of miRNAs in animals. The repression mode in animals acts without slicing the mRNA. It requires the adaptor protein TNRC6 and does not need extensive pairing to the miRNA. Recruited by Ago, TNRC6 interacts with the poly(A)-binding protein (PABPC) associated with the mRNA poly(A) tail and also recruits deadenylase complexes: the PAN2-PAN3 complex and CCR4-NOT complex. Poly(A) tail shortening can lead to either 3'-5' exonucleolytic digestion by the exosome or decapping by the Dcp1-Dcp2 complex. Decapping is followed by 5'-3' exonuclease digestion by Xrn1. The residual cap structure resulting from exosome digestion is cleaved by the scavenger decapping enzyme DcpS. Recruitment of TNRC6 also causes the mRNA to be less efficiently translated. It is due to CCR4-NOT and its recruitment of DDX6, a helicase that binds the decapping complex. DDX6 interacts with eIF4E transporter (4E-T), which competes with eIF4G for binding to eIF4E and enhances both the decay and translational repression of miRNA targets

identification of target mRNAs is to evaluate and rank-order target 3' UTR complementarity to a miRNA by either number of paired nucleotides and/or duplex free energy. However, the various algorithms diversely analyze the RNA folding and promote 5' pairing to a different extent. For this reason, the output from different bioinformatics analyses can vary significantly, and computationally predicted mRNAs need to be validated experimentally to discard false positive and negative targets.^{58,59}

3 | miRNAs IN CRS

CRS is a highly heterogeneous upper airway disease which has a severe impact on the quality of life due to the persistent symptoms of affected individuals.⁶⁰ CRS is classified into two subtypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) which are characterized by distinct cytokines, mediators, and cellular profiles.⁶¹ A different T-lymphocyte subset determines a T-cell

polarization between the Th1 inflammation of the CRSsNP and the Th2-biased eosinophilic inflammation of CRSwNP.⁶² Only a few numbers of studies have investigated the molecular and genetic mechanisms underlying the inflammation process in CRS until the pioneering work of Zhang et al.⁶¹ As they described for the first time, miRNA expression pathways are different between CRSsNP and CRSwNP and seem to be implicated in regulating the inflammation pattern. Compared with the inferior turbinate tissues of the control group, 31 differentially expressed miRNAs (30 down-regulated and 1 up-regulated miRNAs) were found in polyp tissues of eosinophilic CRSwNP and 4 (two down-regulated and two up-regulated miRNAs) were identified in ethmoidal mucosa of CRSsNP. A few years later, Xia et al. also analyzed the differential expression of 7 miRNAs (miR-181b, miR-26b, miR-155, miR-146a, miR-125b, miR-124, and miR-92a) associated with inflammation in 40 clinical samples of chronic sinusitis, with or without nasal polyps, and 5 controls. When compared to the normal control group, miR-125b, miR-155, and miR-146a were up-regulated, while miR-92a, miR-26b,

and miR-181b were down-regulated in all patients with CRS. When compared with CRSsNP, miR-125b and miR-155 were significantly up-regulated while miR-92a, miR-26b, and miR-181b were down-regulated in CRSwNP patients⁶³ (Figure 3A). The differences in miRNAs expression between CRSwNP and CRSsNP highlight that these miRNAs may play a crucial role in endotyping the inflammation of the 2 CRS phenotypes. Thus, the data reveal a relationship between miRNA expressions and the occurrence of CRSwNP.

Furthermore, recent evidence showed that miR-4492 was down-regulated while IL-10 was up-regulated in CRSwNP versus CRSsNP tissues, suggesting that the miR-4492/IL-10 interaction in Jak/STAT signaling pathway could be a possible key mechanism in

CRSwNP.⁶⁴ Consistent with this, a previous study using clinical specimens demonstrated that elevated levels of the pleiotropic cytokine IL-10 have a crucial role in the pathogenesis of CRSwNP.⁶⁵ Moreover, the miR-142-3p and TNF- α were significantly higher in the nasal mucosa of CRSwNP compared with normal human nasal mucosa. miR-142-3p is described to play a decisive role in the expression of pro-inflammatory cytokines in many kinds of cell lines,^{66,67} and these data indicate that it can be involved in the body's inflammatory response through the LPS-TLR-TNF- α signaling pathway in CRSwNP⁶⁸ (Figure 3B). To shed light on the intrinsic mechanisms regulating this complex inflammation process, we performed for the first time a global transcriptome analysis during the mucociliary

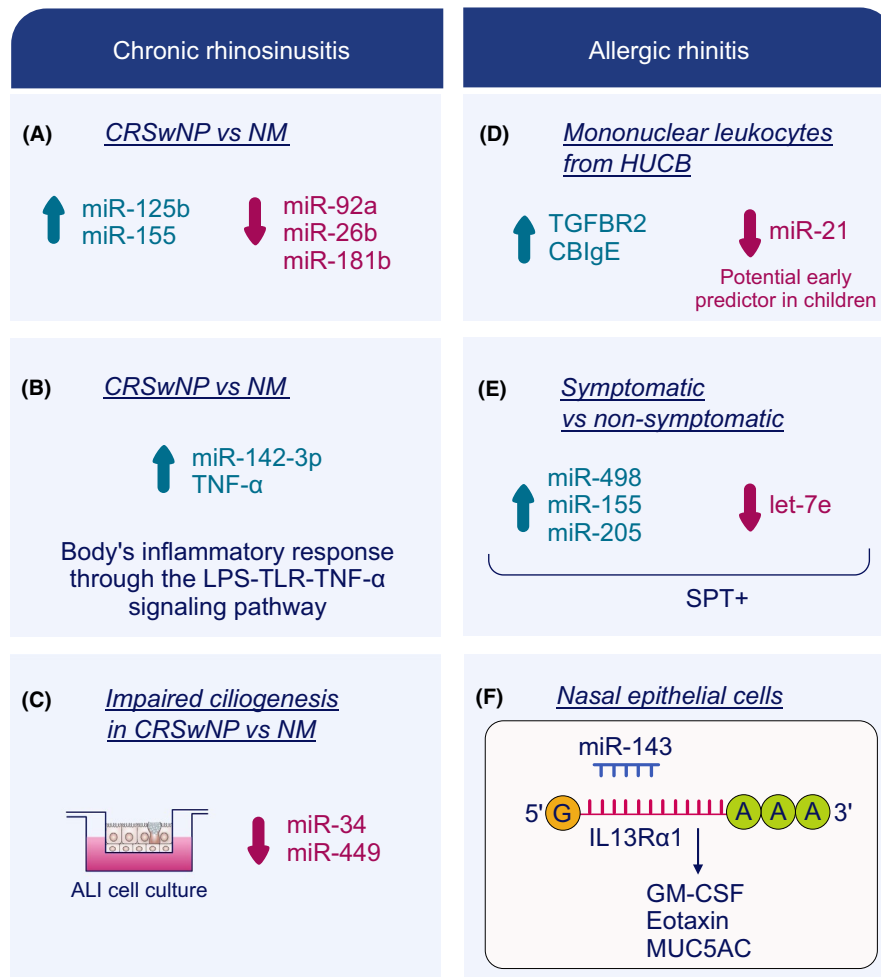


FIGURE 3 Summary of some roles described for miRNAs in CRS and AR. (A) Differentially expressed miRNAs in CRSwNP vs CRSsNP.⁶³ (B) Significantly higher expression of miR-142-3p and TNF- α in the nasal mucosa of CRSwNP compared with normal human nasal mucosa. miR-142-3p is probably involved in the body's inflammatory response through the LPS-TLR-TNF- α signaling pathway in CRSwNP;⁶⁸ (C) Impaired ciliogenesis in CRSwNP presumably produced by miR-34 and miR-449 families;⁶⁹ (D) miR-21 is significantly decreased whereas TGFBR2 expression is increased in HUCB (Human Umbilical Cord Blood) with elevated CBIgE;⁷⁰ (E) The levels of miR-205, miR-155, and miR-498 are significantly increased in AR compared to control and NAR groups in symptomatic subjects, whereas differences in non-symptomatic subjects are less evident; besides, the expression of miR-155 and miR-205 is increased and let-7e decreased in the nasal mucosa of SPT-positive subjects;⁷⁵ (F) miR-143 inhibits IL-13-induced GM-CSF, eotaxin and MUC5AC mRNA expression in nasal epithelial cells.⁷⁶ IFN, interferon; GM-CSF, granulocyte-macrophage colony-stimulating factor; SPT, skin prick test; TGFBR2, transforming growth factor-beta receptor type 2; CBIgE, cord blood immunoglobulin E; 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; NAR, non-allergic rhinitis

differentiation of human epithelial cells from patients with CRSwNP in comparison with healthy nasal mucosa (NM) from control group subjects.⁶⁹ We extracted RNA from both cultures at days 0, 14, and 28 of ALI (air-liquid interface) culture and a global transcriptional analysis was performed by microarray, using the Human Genome U219 for the gene expression, and the miRNA 4.1 Array Plates for miRNA expression. Regarding microRNAs expression, in control-NM cells we detected 52 up- and 47 down-regulated miRNAs at day 14, and 105 up- and 43 down-regulated miRNAs at day 28, compared to day 0 of ALI culture, while in CRSwNP, we identified 143 up- and 45 down-regulated miRNAs at day 14, and 211 up- and 67 down-regulated miRNAs at day 28, compared to day 0 of ALI culture.⁶⁹

Besides, we identified the most represented microRNA families during mucociliary differentiation of both CRSwNP and control-NM ALI. On day 14, we found that some miRNA families were similarly expressed in CRSwNP compared with control NM, such as miR-17, and miR-30 involved in differentiation and proliferation, and in cell cycle division, respectively. On the other hand, other families were differentially represented, such as miR-378, miR-449, and miR-548. Interestingly, miRNAs belonging to the miR-449 families are crucial to trigger multi-ciliogenesis by suppressing cell cycle genes and the Notch pathway in the surface of some vertebrate epithelia.⁶⁹ On day 28, we found that the miRNA families similarly represented in CRSwNP and in the control group were miR-17, miR-188, miR-449, miR-548, and miR-8. Conversely, other families were differentially expressed, such as miR-30, miR-34, and miR-378. We demonstrated for the first time that the genetic transcriptional program responsible for ciliogenesis and cilia function is significantly impaired in CRSwNP epithelium respect to normal epithelium. We suggest that this alteration is due to a different expression profile of miRNAs, particularly of those belonging to miR-34 and miR-449 families⁶⁹ (Figure 3C).

4 | miRNAs IN AR WITHOUT ASTHMA

Recent evidence highlights the emerging roles of miRNAs in allergic diseases such as in the regulation of AR pathogenesis. One of the first investigations was about the association of miRNA expression and children with AR.⁷⁰ This study demonstrated that miR-21 and miR-126 expressions were significantly lower in mononuclear leukocytes from human umbilical cord blood (CB) samples of AR children. miR-21 expression was also correlated to the significant up-regulation of the identified target-gene transforming growth factor-beta receptor 2 (TGFB2) and with elevated CBIgE (Figure 3D). Thus, miR-21 has been proposed as a potential early predictor of AR⁷⁰ (Table S1).

Yu et al. presented one of the first research articles about the difference in miRNA expression profiles between AR patients and non-allergic individuals.⁷¹ They identified by miRNA microarray analysis 421 miRNAs differentially expressed in the nasal mucosa of AR compared with control. They found that 2 miRNAs were significantly up-regulated (hsa-miR-7 and hsa-miR-Plus-E1194), whereas 7 miRNAs (hsa-miR-498, hsa-miR-187, hsa-miR-874, hsa-miR-143, hsa-miR-886-3p, hsa-miR-224, and hsa-miR-767-5p) were

down-regulated in AR compared with control.⁷¹ To further analyze whether some of these differentially expressed miRNAs were useful in endotyping AR, Soujalehto et al. analyzed two subgroups: AR symptomatic and non-symptomatic subjects. Although some discrepancies from previous results, they found elevated levels of miR-155, miR-205, miR-498, and low levels of let-7e in subjects with current AR symptoms (Figure 3E). Compared to individuals with negative SPT, the positive ones showed a high expression of miR-155, which plays an important role in the function of B and T lymphocytes and dendritic cells, and miR-205 is described as a tumor suppressor or an oncogene.^{72,73} Moreover, they showed a decreased level of let-7e, implicated in the regulation of allergic inflammation in bronchial epithelial cells stimulated with IL-4 and tumor necrosis factor-alpha (TNF α).^{74,75}

Beyond the study of the expression profile, attempts have been made to investigate the possible role of miRNAs in the regulation of chronic inflammatory conditions in AR. It was shown that forced expression of miR-143 in nasal epithelial cells, stimulated with IL-13, significantly decreased the mRNA and protein expression of granulocyte-macrophage colony-stimulating factor (GM-CSF), eotaxin, and mucin 5AC (MUC5AC). MiR-143 directly targeted IL-13 receptor α 1 chain (IL13Ra1) gene expression, suppressing cytokines, and mucus production⁷⁶ (Figure 3F) (Table S1).

5 | miRNAs IN UNITED AIRWAY DISEASES

The pathogenesis and the gene regulation of the UAD are unclear, and so far only a few studies have investigated the role of miRNAs in these processes.^{77,78} Two articles from the same group analyzed the miRNAs expression profiles in the nasal mucosa of patients with coexistence of AR and asthma. In the study of 2013 mentioned above, Suojalehto et al. showed that miRNA expression profile, as well as Th2 cytokines levels (IL-4, IL-5, and IL-13), was similar in AR patients with or without asthma.⁷⁵ Likewise, one year later, the authors found 10 miRNAs differentially expressed in asthmatic patients *versus* control individuals (miR-143, miR-187, miR-498, miR-874, and miR-886-3p were up-regulated, whereas let-7e, miR-18a, miR-126, miR-155, and miR-224 were down-regulated) of which miR-155, miR-126, and let-7 have been previously revealed to be pivotal in regulating allergic inflammation^{75,79,80} (Table S2). However, concomitant asthma had only a slight impact on the inflammatory profile of AR.⁸¹ Likely, this discrepancy found in both cases may be explained to the mild severity of asthma or the exposure of the patients to a weak allergy season during the sampling. Taken together, these results indicate that further studies are needed to clarify the interplay between AR and asthma on nasal mucosal miRNA expression. Recently, a functional miR-149 rs2292832 variant was shown to be associated with AR and AR-Asthma (AR-A) compared with the healthy subjects, and also to increase the susceptibility to allergies following the stimulation with an allergen.⁸² rs2292832 has been formerly associated with ischemic stroke, breast, and gastrointestinal cancers in

Asians.^{83,84} Yu et al. also reported data about miR-19a, which is one of the members of the miR-17-92 cluster. They showed that the treatment of AR and AR-A patients with either specific immunotherapy (SIT) or vitamin D3 (VD3) alleviated AR symptoms as well as reduced serum levels of specific IgE and T helper (Th) 2 cytokines. Importantly, it suppressed miR-19a and increased IL-10 in Peripheral blood mononuclear cells (PBMC), which was further improved in those AR patients treated with both SIT and VD3. Thus, they conclude that the administration with VD3 incentives the effect of SIT on suppression of AR via repressing the expression of miR-19a in PBMC.⁸⁵ These results confirmed the data obtained from Geng and coworkers, who showed that the levels of miR-19a were significantly higher in PBMC from AR and AR-asthma patients than in B cells from healthy subjects. Exposure of B cells from these patients to a specific allergen, dust mite extracts, significantly increased the levels of miR-19a and suppressed the expression of IL-10 in B cells. Therefore, it seems that miR-19a could play a role as a novel therapeutic target for the treatment of allergic diseases,⁸⁶ as well as miR-146a, whose expression was found increased after both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) in AR and AR-asthma children. For that, Xi et al. proposed miR-146a as a potential therapeutic target for the improved management of AR⁸⁷ (Table S2).

6 | miRNAs IN EOSINOPHILIC INFLAMMATION

Regarding the association between miRNAs and eosinophilic inflammation in CRSwNP, we only found two articles included in Table 1.^{61,88} In the first one, Ya-Na Zhang and coworkers analyzed the expression of miRNA machinery components in sinonasal mucosa and their potential involvement in CRS. They first examined the mRNA expression of the major miRNA machinery components (Drosha, Dicer, PACT, TRBP, FXR1, and EIF2C2) in sinonasal mucosa. They detected the expression of all the components tested in sinonasal mucosa from normal controls and CRS patients. They concluded that the expression of these proteins is decisive for the metabolism and homeostasis of the miRNAs in sinonasal mucosa under normal and pathological conditions. From immunohistochemical eosinophilic CRSwNP was found a higher expression of PACT protein compared with noneosinophilic CRSwNP. Then, they identified that CD138+ plasma cells were the ones that mainly expressed PACT. The number of CD138+ plasma cells significantly increased in eosinophilic and noneosinophilic CRSwNP as compared with controls and CRSsNP. The relatively abundant expression of PACT in plasma cells but not in other immune cells in CRSwNP suggested that PACT could play an important role in regulating plasma cell function through modulating miRNA production. Unfortunately, the researchers' effort to identify specific changes in miRNA expression in plasma cells in CRS was hampered by technique limitations. In conclusion, this study indicates that the miRNA machinery component PACT may be associated with

plasma cell function and eosinophilic inflammation in CRSwNP⁶¹ (Figure 4A).

In the second study, Xin-Hao Zhang and coworkers studied the pattern of expression and biological role of microRNAs (miRNAs) in CRS, particularly in eosinophilic CRSwNP. They analyzed and compared the global miRNA expression in sinonasal mucosa from controls, (CRSsNP), and patients with eosinophilic CRSwNP using miRNA microarrays. CRSwNP was classified as eosinophilic when percent tissue eosinophils exceeded 10% of total infiltrating cells. In the gene expression study, ethmoidal mucosa or polyp tissues were collected from patients with CRS and inferior turbinate tissues were obtained from control patients during surgery. CRSsNP and eosinophilic CRSwNP exhibited distinct miRNA expression profiles. MiR-125b was specifically up-regulated in eosinophilic CRSwNP.⁸⁸ The function of this miRNA is still unclear. Recent evidence showed that miR-125 targets the UTR region of TNF- α transcripts and regulates negatively P53.^{89,90} To deepen the function of miR-125b, the authors identified by bioinformatics analysis the translational repressor 4E-BP1 as a target. Suppressing the 4E-BP1 protein expression by 4E-BP1 siRNA or miR-125b enhanced type-I interferon (IFN) production in BEAS-2B and human brain microvascular endothelial cells (HBECs). Thus, the suppression of 4E-BP1 may play a critical role in the airway antiviral innate immunity due to the role of IFN in this process⁸⁸ (Figure 4B).

On the other hand, Panganiban and coworkers reported a significant study in the field of AR. They studied circulating miRNAs as noninvasive biomarkers to diagnose and characterize asthma and allergic rhinitis (AR). They identified 30 miRNAs that were differentially expressed among healthy, allergic, and asthmatic subjects. Among asthmatic patients, miRNA expression profiles identified 2 subtypes that differed by high or low peripheral eosinophil levels. Circulating miR-125b, miR-16, miR-299-5p, miR-126, miR-206, and miR-133b levels were most predictive of allergic and asthmatic status. Particularly, expression profiles of circulating miRNAs in asthmatic patients defined 2 subgroups that differed by peripheral eosinophil levels.⁹¹

Therefore, from the data described so far, it seems that miR-125b may be a specific miRNA in the case of eosinophilic CRSwNP^{61,88} and of allergic and asthmatic status.⁹¹ It would be interesting to deepen the studies of the role of eosinophilic inflammation in CRSwNP and AR since until now no many data have been published as well as in asthma (Figure 5).

7 | miRNAs IN EXTRACELLULAR VESICLES

In the last years, it has been described the relevant role in many aspects of physiology and disease, of miRNAs transported into extracellular vesicles (EVs). Since their discovery 30 years ago, a growing interest in the EVs has blossomed. They are small membraned vesicles which can be classified according to their origin and size. EVs can include genetic and protein molecules and deliver their content in cell-cell communication during physiologic

TABLE 1 Role of miRNAs in Chronic Rhinosinusitis (CRS) with (CRSsNP) or without (CRSsNP) nasal polyps.

1st author, year ^{REF}	Disease	N	Gender (Age, year)	Methods	microRNAs	Outcomes	Conclusions
Zhang et al., 2012 ⁶¹	CRSsNP Noneosinophilic CRSsNP Eosinophilic CRSsNP	30 22 22	13F, 17M (27.0) 5F, 17M (37.5) 4F, 18M (42.5)	qRT-PCR Histology Immunohistochemistry	miRNA associated components (Drosha, Dicer, PACT, TRBP, EIF2C2 FXR1)	PACT mRNA is up-regulated in CRSsNP vs CT PACT protein is significantly up- regulated in CRSsNP, (even more in eos CRSsNP) vs CT and CRSsNP	PACT may be associated with the plasma cell function and eosinophilic inflammation in CRSsNP
Zhang et al., 2012 ⁶⁸	CRSsNP, Noneosinophilic CRSsNP, Eosinophilic CRSsNP	43 31 46	25M, 18F 14M, 17F 19M, 25F	miRNA Microarray qRT-PCR <i>In Situ</i> Hybridization Histology and Immunohistochemistry Cell and Nasal Explant Culture	miR-125b	miR-125b is overexpressed in eosinophilic CRSsNP.	The miR-125b-mediated suppression of eIF4E- binding protein 1 may play a role in airway antiviral innate immunity
Xia et al., 2015 ⁶³	CRSsNP and CRSsNP	40	N.A.	RT-qPCR	miR-125b miR-155 miR-92a miR-26b miR-181b	In CRSsNP, miR-125b and miR-155 are significantly up-regulated and miR-92a, miR-26b, and miR-181b are down-regulated vs CRSsNP	Various inflammation severities may lead to the differential miRNA expression in CRS
Li et al., 2019 ⁶⁴	CRSsNP, CRSsNP	39 61	27M (41), 12F (20–65) 38M (44), 23F (23–63)	miRNA-seq DEG screening qRT-PCR	miR-4492	miR-4492 is down-regulated and IL-10 is up-regulated in CRSsNP vs CRSsNP	miR-4492/IL-10 interaction in the Jak/STAT signaling pathway may be one of the key mechanisms in CRSsNP
Qing et al., 2019 ⁶⁶	CRSsNP	20	N.A.	qRT-PCR Enzyme-Linked Immunosorbent Assay	miR-142-3p	miR-142-3p and TNF- α overexpression in CRSsNP	miR-142-3p regulates inflammatory cytokines by Inducing TNF- α Expression
Callejas et al., 2020 ⁶⁹	CRSsNP	7	5M, 2F (53 $\pm$ 6.0)	ALI cell culture mRNA and miRNA Microarray qRT-PCR	miR-34 miR-449	Differential microRNA expression during mucociliary differentiation of CRSsNP vs NM	Down-regulation of miR-34 and miR-449 families presumably produce an impaired ciliogenesis in CRSsNP

Abbreviations: EIF2C2, Argonaute 2/ eukaryotic translation initiation factor 2C; 2; eos, eosinophilic; F, female; FXR1, Emerging data support fragile X mental retardation protein 1; M, male; N.A., Not Available; NM, Normal Mucosa; PACT, Protein Activator of the interferon-induced protein kinase; qRT-PCR, quantitative Real-Time Polymerase Chain Reaction; seq, sequencing; DEG, Diethylene Glycol; TNF, Tumor Necrosis Factor; TRBP, Human immunodeficiency virus transactivating response RNA-binding protein.

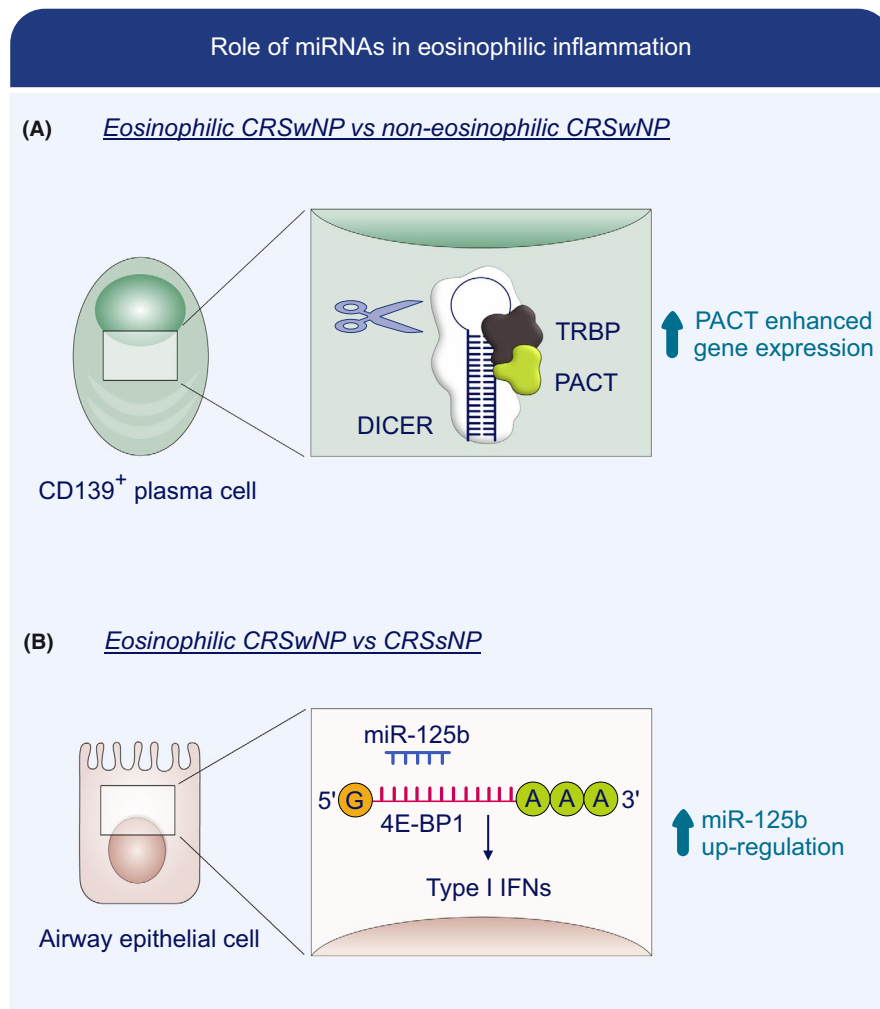


FIGURE 4 Role of microRNAs in eosinophilic inflammation. (A) CD138⁺ plasma cells showed in eosinophilic CRSwNP a higher expression of PACT (miRNA machinery components) protein compared with noneosinophilic CRSwNP.⁶¹ (B) CRSsNP and eosinophilic CRSwNP exhibited distinct miRNA expression profiles in sinonasal mucosa. MiR-125b was specifically up-regulated in eosinophilic CRSwNP. Suppressing the 4E-BP1 protein expression by 4E-BP1 siRNA or miR-125b enhanced type-I interferon (IFN) production in BEAS-2B and human brain microvascular endothelial cells (HBECs)⁸⁸

miRNAs in CRS		miRNAs in AR
- Regulating the occurrence of CRSwNP - Regulating the mucociliary differentiation of epithelial cells from patients with CRSwNP and control-NM	Regulating the eosinophilic inflammation pattern	- Role as potential early predictor - Differential expression in EVs from AR patients compared with controls

FIGURE 5 miRNA biological processes in upper airway inflammation, allergic rhinitis (AR), and chronic rhinosinusitis (CRS). Venn diagrams show the main biological processes in which miRNAs are involved in CRS and AR. Both share the miRNA regulation of eosinophilic inflammatory pattern mechanisms. CRSwNP, CRS with Nasal Polyps; EVs, Extracellular Vesicles; NM, Nasal Mucosa

and pathologic conditions.⁹² Previous reports implicate miRNAs from EVs in a large number of biological processes and mechanisms as well as in diseases.^{93,94} A few numbers of papers describe the role of miRNAs from EVs in AR patients. Wu et al for the first time characterized the miRNA content of EVs in AR patients compared to healthy control subjects.⁹⁵ From a screening of 366 probes for human miRNAs, 21 EV miRNAs were up-regulated and 14 miRNAs were under-regulated significantly in nasal mucus from AR patients when compared to healthy individuals. Particularly, miR-203 was significantly increased, while microRNA-875-5p was decreased in patients with AR, and both involved in the salivary secretion pathway. Bioinformatics analysis demonstrated that EV miRNAs modulated a regulatory function in AR by the 32 Kyoto Encyclopedia of Genes and Genomes (KEGG) biological processes significantly enriched among differentially expressed miRNAs. The B-cell receptor signaling pathway, the natural killer cell-mediated cytotoxicity, the T-cell receptor signaling pathway, the RIG-I-like receptor signaling pathway, the Wnt signaling pathway, endocytosis, and salivary secretion were among the biological processes.⁹⁵ On the other hand, Luo and coworkers showed that miR-146a derived from the EVs of RPMI2650 cells (an airway epithelial cell line) could induce the expression of IL-10 in monocytes. The inducible IL-10+ monocytes showed an immune suppressor effect on the activities of CD4+ effector T cells and the Th2 polarization in a mouse AR model with the Ovalbumin (OVA). Thus, they conclude that miR-146a has the potential in the treatment of allergic disorders, such as AR.⁹⁶

8 | miRNAs IN PLASMA

More promising outcomes were obtained by the previously mentioned work by Panganiban et al. They found that 30 miRNAs over the 420 analyzed were differentially expressed in plasma from healthy, allergic, and asthmatic subjects. They demonstrated for the first time that subsets of circulating miRNAs (miR-125b, miR-16, miR-299-5p, miR-126, miR-206, and miR-133b) were exclusively expressed in patients with AR and asthma.⁹¹ Almost all of these miRNAs targeted predicted genes involved in inflammation pathways such as the mitogen-activated protein kinase (MAPK) signaling, which is well known in the pathogenesis of AR and asthma,^{97,98} as well as the phosphoinositide 3-kinase-Akt pathway, which is another crucial signaling cascade in TH2 inflammation.^{99,100} Thus, these results suggest their potential use as noninvasive biomarkers to diagnose AR and asthma as well as to characterize asthma subtypes. In another study, Hirai et al. screened 84 miRNAs for expression levels in patients with asthma chronic obstructive pulmonary disease overlap (ACOPD) or asthma using a quantitative real-time PCR array. They identified miR-15b-5p as the most accurate miRNA for the discrimination of patients with ACO and proposed it as a potential marker for identifying this kind of patient.¹⁰¹

9 | CLINICAL PERSPECTIVE

Due to their stability, miRNAs have been early recognized as potential biomarkers in many disease diagnostics. Currently, preclinical studies on cancer are describing the miRNAs roles in early tumor detection, stratification, and monitoring.¹⁰²⁻¹⁰⁴ For instance, to evaluate their predictive value in detecting endometrial cancer an on-going clinical trial in the United Kingdom is determining miRNAs in the urine of cancer and healthy patients. The principal outcome is to test miRNAs as an early biomarker and to determine how well they correlate with final histology, that is, can miRNAs determine the subtype of endometrial cancer.¹⁰⁵ Besides, the significance of miRNAs is studied not only in the field of cancer but also in any kind of diseases such as in HIV and tuberculosis (TB) infections. Nowadays, circulating miRNA (in plasma and/or exosomes) patterns are being evaluated to discover whether they might be applicable as potential biomarkers in the prediction and prognosis of immune reconstitution syndrome (IRIS) in HIV/TB co-infected patients.¹⁰⁶ Likewise, also anti-miRNAs therapeutics have reached clinical development, that is, anti-miRNAs targeted at miR-122 for treating hepatitis C infection by down-regulation of the replication of the hepatitis C virus RNA genome.¹⁰⁷

Indeed, the clinical application of miRNAs also in inflammatory upper diseases would definitively change the diagnosis, prognosis, and treatment approaches for AR and CRS. Especially in AR disease, we found breakthroughs. As mentioned above, allergic rhinitis is characterized by typical miRNAs expression profiles. Among the possible miRNAs candidates for AR biomarkers, miR-21 was one of the firsts described to be useful for the diagnosis of AR in newborn,⁷⁰ being one of the most prominent miRNAs implicated in the genesis and progression of human tumors, especially in cancer proliferation,¹⁰⁸ progression,¹⁰⁹ and anti-apoptosis.¹¹⁰ On the other hand, miR-181a levels seem to be an encouraging predictor of disease severity in childhood AR.¹¹¹ Compared with healthy controls, children with AR had significantly higher serum levels of osteopontin (OPN) and lower serum levels of miR-181a, which has been described to be related to OPN expression in hepatocellular cancer and atherosclerosis.^{112,113} Successful biomarkers should be safe and easy to measure, cheap, and able to give accurate results. Moreover, they should be easily applied in clinical practice.¹¹⁴ Because of their characteristics, miRNAs are considered good biomarkers for any future medical usage. Thus, the data about miR-21 and miR-181a in the early age AR patients seem to be promising for the study of this disease. Other findings also demonstrated that nasal mucosa miR-221 and miR-142-3p expression levels were elevated and could represent novel and promising biomarkers with a sensitivity of 81% and a specificity of 65% for AR diagnosis. MiR-142-3p is described as a hematopoietic specific miRNA whose overexpression reinforces the degranulation of mast cells.¹¹⁵ miR-221 is also known to mediate mast cell degranulation, as well as the cytokine production and cell adherence in a mast cell-specific and activation-dependent way.¹¹⁶ Moreover, miR-221 expression was also correlated with disease

severity of AR.¹¹⁷ miR-126-5p, miR-19a-5p, and miR-26a-5p are involved in mast cell degranulation and cytokine production,¹¹⁸ regulation of immunity,¹¹⁹ and pathogenesis of the inflammation-related disease¹²⁰, respectively. Jia et al. also described that a combination of these miRNAs could also be associated with AR diagnosis, proposing their expression profile as a novel biomarker.¹²¹

Interestingly, recent evidence indicates that endothelial miR-1 regulates eosinophil trafficking in the setting of allergic airway inflammation, showing a therapeutic potential in asthmatic patients and patients with CRS. Serum miR-1 levels had inverse correlations with sputum eosinophilia, airway obstruction, and the number of hospitalizations in asthmatic patients and sinonasal tissue eosinophilia in patients with CRS. Moreover, miR-1 levels were down-regulated by IL-13, a prototypic T2 cytokine, in human lung and endothelial cells.¹²²

On the other hand, the effects of miRNAs administration *in vivo* have been studied above all in AR where miRNAs can be considered as a potential mechanism to modulate gene expression of Th2 inflammation. AR was induced by serum ovalbumin (OVA) in mice, and two groups were treated with a miR-135a mimic and a mimic control, respectively. Following intranasal miR-135a application in OVA-sensitized mice, the mRNA and protein expression levels of GATA-3 and IL-4 were reduced.¹²³ Similarly, one year later, Deng et al. demonstrated that the miR/135a administration to OVA-sensitized mice appeared to balance the ratio of type 1 T-helper cells (Th1) to type 2 (Th2) cells by increasing and decreasing the percentage of Th1 and Th2 cells, respectively. The miR-135a corrected the Th1/Th2 imbalance in the AR mice.¹²⁴ Besides, miR-135a also appeared to strongly suppress specifically the infiltration of eosinophils in the Mast cells (MCs) into the nasal mucosa, suggesting that its influence is modulated through the regulation of GATA-3 in these cells.

Several studies are needed to identify possible miRNA biomarkers and function also in the CRS investigations to get successful diagnosis and treatment.

Hence, in many studies and diseases, sufficient evidence supports circulating miRNAs in body fluids as potential noninvasive diagnostic and prognostic biomarkers. Indeed, this will lead to the development of future diagnostic tests from easily assessable biofluids. However, the field still lacks consistency and despite promising results; an effort is needed to overcome several limitations of the investigations. Precise quantification of circulating miRNAs, differences in methodology, lack of standard methods for normalization, and the difficulty to discriminate among closely related miRNAs are some of the most relevant challenges.^{125,126}

10 | CONCLUSIONS

Despite the growing number of studies about the miRNAs expression and related pathway in CRS and AR, there is still a need to investigate their specific role in airway upper diseases. The results from AR studies indicate some miRNAs as the best candidate to continue on exploring their function pathways and therapeutic effects, which have not been established completely. miR-21

expression in CB would be a regulator of IgE production and development⁷⁰ of AR while circulating miR-125b, miR-16, miR-299-5p, miR-126, miR-206, and miR-133b are uniquely expressed in patients with AR and asthmatic patients and define 2 subgroups that differ by peripheral eosinophil levels.⁹¹ On the other hand, the number of published studies on miRNA in CRS is limited; thus, further studies are needed to explore more this field but in the nose and under the concept of United Airways. In our recent study, we provide the molecular basis of sinonasal mucociliary differentiation and we demonstrated a significant transcriptional impairment during differentiation of CRSwNP epithelium. We especially identified the altered expression of those microRNAs belonging to mir-34 and mi-449 families.⁶⁹ Thus, further *in vitro* or *ex vivo* experiments are required to demonstrate the real action of these miRNAs and the expression of their targets.

CONFLICT OF INTEREST

Dr. Tubita, Dr. Callejas-Díaz, Dr. Roca-Ferrer, Dr. Marin, Dr. Liu, and Dr. Wang have nothing to disclose. Dr. Mullol reports personal fees and other from SANOFI-GENZYME & REGENERON, and NOVARTIS & GENENTECH; grants and personal fees from MYLAN-MEDA PHARMA and URIACH GROUP; personal fees from MITSUBISHI-TANABE, MENARINI, ASTRAZENECA, GSK, and MSD, outside the submitted work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Supplementary Table 1. Role of miRNAs in allergic rhinitis (AR) without comorbid asthma

1 st author, year REF	Disease	N	Gender (Age, yr)	Methods and cells/tissues	microRNAs	Outcomes	Conclusions
Wang et al., 2019 s1	AR	30	9F 21M (21–52)	qRT-PCR WB, ELISA Flow Cytometry T cells suppression/PBMC from blood cells	miR-202-5p	<i>In vitro</i> , miR-202-5p promotes Tregs differentiation via targeting MATN2.	MiR-202-5p/MATN2 are associated with regulatory T-cells differentiation and function in allergic rhinitis.
Wang et al., 2019 s2	AR	20	10F, 10M (28.7)	qRT-PCR WB Transfection ELISA/Human primary NECs	miR-15a-5p	ADRB2 is directly targeted by miR-15a-5p, and miR-15a-5p inhibits IL-13-induced expression of GM-CSF, eotaxin, and MUC5AC in NECs	ADRB2 is negatively regulated by miR-15a-5p, which inhibits IL-13-induced nasal epithelial inflammatory responses
Zeng et al., 2019 s3	AR	20	11F (9) 9M (7-12)	Transfection Animal models T cells suppression qRT-PCR/ CD4 ⁺ T cells and Tregs PBMCs	miR-181a miR-155	miR-181a up-regulates the release of IL-10 and TGF- β , whereas the miR-155 promotes Treg differentiation in CD4 ⁺ T cells.	miR-181a and miR-155 are closely correlated with the proliferation and function of Tregs in AR, providing new potential treatment target
Chen et al., 2010 70	AR children with H risk and L risk to elevated CBIgE	10	N.A. (6.03±0.03)	miRNA Microarray qRT-PCR/ Mononuclear leucocytes from HUCB	miR-21 miR-126	miR-21 and miR-126 expression is significantly lower in monocytes from AR children	Lower miR-21 expression in CB and increased TGFBR2 expression is associated with antenatal IgE production and development of AR

1 st author, year ^{REF}	Disease	N (Patients or mice)	Gender (Age, yr)	Methods and cells/tissues	microRNAs	Outcomes	Conclusions
Zhou et al., 2020 ^{S4}	AR	41,P	16F ,25M (15.9 ± 21.2)	qRT-PCR Transfection Histology BALB/c mice/ HEK293T cells serum	miR-223-3p	miR-223-3p levels increased significantly in both allergic rhinitis patients and allergic rhinitis mice	miR-223-3p plays an important role in regulating the pathology and symptoms of AR by targeting INPP4A.
Liu et al., 2020 ^{S5}	AR	110,m	110F	qRT-PCR, WB, Flow cytometry Immunohistochemistry, ELISA, BALB/c mice model /serum, AR and normal mucosa tissues	miR-345-5p	Upregulated miR-345-5p inhibited inflammatory response, nasal fibrosis and apoptosis of nasal epithelial cells by suppressing the TLR4/NF-κB pathway in mice with AR	miR-345-5p play a crucial role in alleviating the inflammatory response in mice with AR by inhibiting the TLR4/NF-κB pathway
Zhu et al., 2020 ^{S6}	AR	10,P 48,m	N.A. 48M(from 6 to 8 weeks)	mouse AR model, qRT-PCR, WB, Transfection, RNA pull-down assay FISH/ nasal mucosa and blood of AR patients and mice	miR-495	CircHIPK3 and LncGAS5 induced the upregulation of Th2 cell- specific transcript factor GATA-3 via modulating their common target miR-495.	The interactions among CircHIPK3, LncGAS5, and miR-495 play a critical role in the regulation of Th2 differentiation in AR.
Liu et al., 2020 ^{S7}	AR	40,m	40F	BALB/c mice qRT-PCR, Immunohistochemistry, ELISA/ Spleen cells, nasal mucosa and plasma	miR-17-5p	The overexpressed circDdx17 inhibited the expression of miR-17-5p and further alleviated the condition of AR	circDdx17 could be considered as a candidate in the prevention of AR.

1 st author, year ^{REF}	Disease	N(Patients, mice or rats)	Gender (Age, yr)	Methods and cells/tissues	microRNAs	Outcomes	Conclusions
Cui et al., 2019 ^{S8}	AR	8,m	N.A. Six-week-old	qRT-PCR WB Bisulfite sequencing PCR / TMNE cells	miR-199-3p	The injection of a miR-199-3p antagomir successfully attenuated the symptoms of AR	miR-199-3p–Dnmt3a–STAT3 signalling pathway is involved in OVA-induced AR
Chen et al., 2019 ^{S9}	AR	10,m	10M Five-week-old	qRT-PCR, WB, Luciferase activity assay Transfection, ELISA/ Splenocyte culture	miR-466a-3p	miR-466a-3p negatively regulated GATA-3 expression in allergic rhinitis mice, indicating the participant of Th2-cell responses in allergic rhinitis	miR-466a-3p contributes to the pathogenesis of allergic rhinitis in vivo
Gao et al., 2018 ^{S10}	AR	25,P	N.A.	MiRNA Array, qRT-PCR, ELISA, Transfection, WB, Luciferase reporter assay/ nasal mucosa; JME/CF15 and 293T NEC line	miR-16	miR-16 was downregulated in AR and IL-13 treated JME/CF15 cells, and overexpression of miR-16 inhibited inflammatory response by blocking the activation of IKK β /NF- κ B signaling pathways	miR-16/IKK β /NF- κ B axis might represent a beneficial way of regulating nasal inflammation and preventing the development of AR.
Xiao et al., 2018 ^{S11}	AR			qRT-PCR, Transfection ELISA, WB, Immunofluorescent staining / human mast cell line HMC-1	miR-302e	miR-302e was down-regulated in HMC-1 cells in response to PMA/A23187. MiR-302e overexpression limited allergic inflammation through inhibition of NF- κ B activation	miR-302e may be a promising therapeutic target for the treatment of allergic diseases, such AR.

1 st author, year ^{REF}	Disease	N(Patients, mice or rats)	Gender (Age, yr)	Methods and cells/tissues	microRNAs	Outcomes	Conclusions
Wang et al., 2018 ^{S12}	AR	30,m	30F Five-week-old	qRT-PCR WB, ELISA, Immunohistochemical and tunel staining, RIP/ mice plasma and HNEpC	miR-375	Overexpression of miR-375 or knockdown of JAK2 (direct target) could efficiently suppress the increased epithelia apoptosis of nasal mucosa and inflammation in a JAK2-dependent manner	miR-375 could prevent nasal mucosa cells from apoptosis and ameliorate allergic rhinitis via inhibiting JAK2/STAT3 pathway
Jia et al., 2018 ¹²¹	AR	8,P	5F, 3M 20.88 ± 5.79	miRNA microarray qRT-PCR (validation in 48 patients), / nasal mucosa	miR-126-5p, miR-19a-5p and miR-26a-5p	miR-126-5p, miR-19a-5p and miR-26a-5p were up-regulated in AR patients vs controls and were independent predictive factors for AR risk	miRNA profiles distinguish AR patients from controls and the combination of miR-126-5p, miR-19a-5p and miR-26a-5p could serve as novel biomarker for AR risk
Hou et al., 2017 ^{S13}	AR	66,m	66M Eight-week-old	RNA sequencing, qRT-PCR, Bioinformatics analysis /nasal mucosa	miR-124-3p/5p, miR-133b-5p, miR-133a-3p/5p, miR-384-3p, miR -181a-5p, miR -378a-5p and miR -3071-5p	IB treatment significantly downregulated IL-4Rα and PGE D2 synthase, whereas upregulated the leukemia inhibitory factor, A20 and nuclear receptor subfamily 4. miR-124-3p/5p, -133b-5p, -133a-3p/5p, -384-3p, -181a-5p, -378a-5p and -3071-5p significantly increased	miR-16/IKKβ/NF-κB axis might represent a beneficial way of regulating nasal inflammation and preventing the development of AR.

1 st author, year ^{REF}	Disease	N(Patients, mice or rats)	Gender (Age, yr)	Methods and cells/tissues	microRNAs	Outcomes	Conclusions
Yu et al., 2017 ^{S14}	AR	32,m	32F Eight-week-old	MicroRNA synthesis, AR ARC57BL/6 mice model, qRT-PCR/ mouse nasal lavage fluid, nasal mucosa	miR-let-7a	miR-let-7a increased the number of nose scratching events, promoted nasal mucosal eosinophilia and goblet cell hyperplasia, increased IL5, IL13. Mice- miR-let7-treated enhanced OPN expression.	miR-let-7a can promote the development of AR partly by regulating OPN expression
Xiao et al., 2017 ^{S15}	AR	80,m	N.A. Eight-week-old	AR BALB/c mice model qRT-PCR, IgE and cytokines measurement Histological analyses Transfection, WB/ plasma and nasal mucosa	miR-133	Upregulation of miR- 133b ameliorated the pathology of AR through inhibition of inflammatory responses, which includes reduced serum OVA-specific IgE concentration, eosinophils and mast cells infiltration and proinflammatory cytokines levels	Upregulation of miR- 133b in nasal mucosa may be a potential therapeutic approach for the treatment of AR
Liu et al., 2016 ^{S16}	AR	25,P children	12F, 13M (65.2 ± 34.0 months)	qRT-PCR, ELISA/ serum	miR-181a	AR children had higher serum levels of OPN and lower of miR-181a vs controls. OPN positively correlated with Th2 cytokine and negatively correlated with Th1 cytokine. miR-181a level had a negative correlation with IL-4/IL-5 and positive correlation with IFN-γ/IL-12	The OPN protein and miR-181a levels may serve as predictors of disease severity in childhood AR and appear to be promising targets for modulating AR.

1 st author, year ^{REF}	Disease	N(Patients, mice or rats)	Gender (Age, yr)	Methods and cells/tissues	microRNAs	Outcomes	Conclusions
Liu et al., 2016 ^{S17}	AR	6,m 10,P	6M (Six-week-old) N.A.	BALB/c mice model, ELISA, T cell proliferation assay, Flow cytometry/ serum, nasal mucosa and mouse bone marrow cells	miR-146a	The co-administration with miR-146a significantly enforced the effect of OVA- specific immunotherapy on inhibition of AR inflammation in the nasal mucosa. miR-146a induced TGFβ in dendritic cells	miR-146a may have therapeutic potential to be used in the immunotherapy of allergic diseases
Luo et al., 2015 ^{S18}	AR	6-9,m 10,P	6-9M N.A. N.A.	qRT-PCR,WB, ELISA, nasal allergy BALB/c mice model Flow cytometry Transfection/ Human NEc, CD14+ CD16- Mos from PBMCs, nasal mucosa	Exosome miR-466a	miR-146a was markedly lower in NEc of patients with AR vs controls. Exposure to Th2 cytokines suppressed the levels of miR-146a. NEc-derived miR-146a up regulated the expression of IL-10 in Mos.	NEc express miR-146a, the latter is capable of inducing IL-10 expression in Mos, which suppress allergic reactions in the mouse nasal mucosa
Quin-Deng et al., 2015 ¹²⁴	AR	36,m	36M (Six-eight- week-old)	AR BALB/c mice mode, Vector administration qRT-PCR, Flow cytometry, Histology/ Blood and nasal mucosa	miR-135a	miR-135a treatment reduced serum IgE concentration, balanced the Th1/Th2 ratio, and induced higher and lower expression of T- bet and GATA-3 in nasal mucosa, respectively.	This study provides a foundation for the use of intranasally administered miR-135a- containing vectors for treatment of allergen- induced inflammation.

1 st author, year ^{REF}	Disease	N(Patients, mice or rats)	Gender (Age, yr)	Methods and cells/tissues	microRNAs	Outcomes	Conclusions
Liu et al., 2015 ^{S19}	SAR	9,P	4F,5M N.A.	MiRNA Array DEGs Bioinformatics analysis/ CD4+ T cells	miR-139, miR-101, miR-29A, miR-181 miR-200 miR-29A	miR-139, miR-101, miR-29A, and miR-181 could target FOS; miR-200 and miR-29A could target KLF4; miR-101 and miR-200 could target DUSP1; miR-139 and miR-181 could target JUN and CD163, respectively.	FOS, JUN, and DUSP1 could be used as candidate targets for the treatment of SAR during the pollen season, while KLF4 and CD163 could be used as candidate targets outside the pollen season
Wu et al., 2015 ^{S20}	Severe AR	54,P	29F, 25M 25.4 (6-36)	Centrifugations, Flow Cytometry, microRNA expression profiling, bioinformatics analysis/ Nasal mucus	miR-30-5p and miR-199b-3p miR-874 miR-28-3p miRNA-203 miRNA-875-5p	MiR-30-5p and miR-199b-3p were increased in EVS from nasal mucus vs controls, while miR-874 and miR-28-3p were down-regulated. miRNA-203 was increased in AR patients, while miRNA-875-5p decreased in AR patients	This study demonstrated that vesicle miRNA may be a regulator for the development of AR
Tang et al., 2015 ^{S21}	AR	N.A., m	M (Six-eight- week-old)	Sequencing, qRT-PCR, Transfection, ELISA Luciferase reporter assay, Flow cytometry/ BMDCs	miR-106b	Surface marker expression was upregulated after the transfection of an miR-106b inhibitor and the proportion of GATA-3 T cells was increased among CD4+ T cells that were cocultured with miR-106b inhibitor-pretreated BMDCs	miR-106b negatively regulates the pro-allergic properties of BMDCs and subsequent Th2 polarization upon OVA stimulation and might represent a promising therapeutic target for allergic inflammation

1 st author, year ^{REF}	Disease	N(Patients, mice or rats)	Gender (Age, yr)	Methods and cells/tissues	microRNAs	Outcomes	Conclusions
Hou et al., 2015 ^{S22}	SAR	15,P	8F, 7M. 34.7 (18–52)	Measurement of Immunoglobulin Titer, qRT-PCR/ serum	miR-223 let-7b	Serum miR-223 was up-regulated in postseason vs preseason samples. let-7b was more down-regulated in postseason than in preseason samples from the placebo group; A significant decrease in circulating let-7b was observed in the subjects who developed symptoms	The changes of miR-223 would reflect the exposure to antigen in the pollen season. Changes of let-7b during cedar pollen season in asymptomatic, sensitized subjects may play a role in the pathogenesis of AR
Teng et al., 2015 ⁷⁶	AR NAR	23,P 18, P	10F, 13M 33.9 (21–61) 7F, 11M 31.4 (23–57)	qRT-PCR, ELISA, WB, Luciferase activity assay/ NECs	miR-143	The forced expression of miR-143 significantly decreased the mRNA and protein expression levels of GM-CSF, eotaxin and MUC5AC in IL-13-stimulated NECs. miR-143 directly targeted and suppressed IL13Rα1 gene expression	miR-143 regulation of IL-13-induced inflammatory cytokine and mucus production in NECs from AR patients probably partly depends on inhibition of IL13Rα1. The IL13Rα1 signaling pathway may be a potential target for the prevention and treatment of AR by miR-143
Yu et al., 2013 ^{S23}	AR	N.A.	N.A.	Lentivirus Production and Transfection Luciferase Assays, qRT-PCR, WB/ HMC-1	miR-143	Compared to the control, the target gene IL-13Rα1 was less expressed in HMC-1 transfected with miR-143	miR-143 directly targets IL-13Rα1 and suppresses IL-13Rα1 expression in HMC-1 cells. miR-143 may be associated with allergic reaction in human mast cells

1 st author, year REF	Disease	N	Gender (Age, yr)	Methods and cells/tissues	microRNAs	Outcomes	Conclusions
Shaoqing et al., 2011 S24	AR	8,P	5F, 3M 35 (22–50)	MicroARRAY, qRT-PCR, Bioinformatics analysis /inferior turbinate nasal mucosa	miR-7, miRPlus-E1194, miR-498, miR-187, miR-874, miR-143, miR-886 –3p, miR-224, miR-767–5p	The miRNA microarray chip analysis identified 421 miRNAs differentially expressed in the nasal mucosa of AR, and a total of 9 miRNAs were identified in the AR group with twofold change compared with control samples	Many miRNA expressions were altered in AR and differentially expressed miRNAs appear to be involved in the development of AR
Ruan et al., 2020 S25	AR	37	20F 17M (67.5 ± 38.2)	qRT-PCR ELISA/ serum and mucosa tissues	miR-223	miR-223 is increased and IL-35 was decrease in the serum of children with AR. The levels of miR- 223 and IL-35 are related to Th1/Th2 cytokines.	miR-223 and IL-35 have a potential role as molecular target for the treatment of AR.

ABPA: Allergic bronchopulmonary aspergillosis; AR: Allergic rhinitis; BMDCs: Bone marrow-derived dendritic cells; CB: Cord Blood; ChIP: Chromatin immunoprecipitation; CT: Control; DEGs: Differentially-expressed genes; EVs: Extracellular Vesicles; F: Female; M: male; FISH: Fluorescence in situ hybridization; GM-CSF: Granulocyte–macrophage colony-stimulating factor; H: high; HMC-1: Human Mast Cells-1;HUCB: Mononuclear leucocytes from human umbilical cord blood; HNEpC: Human nasal mucosa cells; IB: Ipratropium bromide; Ig: Immunoglobuline; L: Low; m:Mice; Mos: Monocytes; MUC5AC: Mucin 5AC; N.A. : Not Available; NAR: Non- Allergic Rhinitis; NECs: Nasal epithelial cells; nNO: Nasal Nitric Oxide; P:Patients; PBMC: Peripheral blood mononuclear cells; PGE: Prostaglandin; qRT-PCR: quantitative Real-Time Polymerase Chain Reaction; R: Rats; RIP: Rna Immunoprecipitation; RNAi: RNA interference; SAR: Seasonal allergic rhinitis; SCIT: Subcutaneous immunotherapy; SIT: Specific Immunotherapy; SLIT: Sublingual Immunotherapy;SPT: Skin Prick Test; TGFB2: Transforming Growth Factor Beta Receptor 2; Th: T Helper; TMNE: Transfected mouse nasopharyngeal epithelial; VD3: Vitamin D3.

Supplementary Table 2. Role of miRNAs in allergic rhinitis (AR) with comorbid asthma

1 st author, year REF	Disease	N	Gender (Age, yr)	Methods cells/tissues	microRNAs	Outcomes	Conclusions
Suojalehto et al., 2013 75	AR,	60	33F, 27M (33.2±1.4)	IgE, nNO measurements	miR-205, miR-155, miR-498 let-7e	miR-205, miR-155, and miR-498 are significantly increased in AR vs CT and NAR. Let-7e is significantly downregulated in AR+asthma vs CT and NAR nonsymptomatic	miR-155, miR-205, miR- 498, and let-7e may be important in the allergic inflammation present in nasal mucosa
	AR + asthma,	34	19F, 15M (32.5±1.1)	SPTs			
	NAR	40	33F, 7M (33.2±1.5)	Histology qRT-PCR/ nasal biopsies			
Suojalehto et al., 2014 81	Asthma - AR	21	N.A.	IgE, Nno measurements	miR-18a, miR-126, let-7e, miR-155, miR-224 miR-498, miR-187, miR-874, miR-143, miR-886-3p	Downregulation of miR- 18a, miR-126, let-7e, miR-155, and miR-224 and upregulation of miR-498, miR-187, miR-874, miR- 143, and miR-886-3p are observed in asthmatic patients vs controls	The differences in miRNA expression are mainly similar in asthmatics with and without AR
	Nonpersistent Asthma + AR	50		SPTs			
	Persistent Asthma + AR	46		Histology qRT-PCR/ nasal biopsies			
Panganiban et al., 2016 91	Asthma	35	21F, 14M (43.9±2.47)	qRT-PCR Bioinformatics/ plasma	miR-125b,miR-16, miR-299-5p,miR- 126,miR-206, and miR-133b	Circulating miR-125b, miR-16, miR- 299-5p, miR-126, miR-206, and miR-133b are uniquely expressed in patients with AR and asthmatic patients	Expression profiles of circulating miRNAs in asthmatic patients define 2 subgroups that differ by peripheral eosinophil levels.
	AR	25	14F, 11M (39.8±3.12)				
Luo et al., 2016 87	AR ± asthma	24	10F, 14M (6.5±2.7)	qRT-PCR, ELISA, WB Flow Cytometry/ nasal mucosa, PBMCs, serum, and NECs	miR-146a	The relative expression of miR-146a and Foxp3 mRNA was increased after both SCIT and SLIT (P<0.01)	miR-146a is a potential therapeutic target for the improved management of AR.

1 st author, year REF	Disease	N	Gender (Age, yr)	Methods cells/tissues	microRNAs	Outcomes	Conclusions
Yan et al., 2020 S26	AR, asthma	12	N.A.	expression profiling arrays/ nasal and bronchial epithelia	predicted miRNAs miR-195-5p, miR-16-5p, and miR-125a-3p.	The co-expressed DEGs of BPIFA1, CCL26, CPA3, and CST1, together with corresponding predicted miRNAs (miR-195-5p, miR-16-5p, and miR-125a- 3p) were significantly correlated with rhinitis and asthma	The top 5 corresponding predicted miRNAs of each co-DEGs could be underlying biomarkers or therapeutic targets for rhinitis-related asthma, especially miR-195-5p, miR-16-5p, and miR-125a- 3p.
Daniel et al., 2018 S27	AR Asthma	20 16	10F, 10M (38.9 ± 3.6) 13F, 3M (39.9 ± 3.66)	Nanostring microarray, qRT- PCR/ PBMc	miR-155	Mir-155 was differentially expressed in allergic T- cells exposed to dust mite extract compared to in non-allergic cells and it is inhibited by glucocorticoids	miR-155 may play a role in mediating allergic inflammation in T-cells and could be an antiinflammatory target of steroids
Wu et al., 2018 S28	Asthma AR ABPA	53 15 10	33F, 20M (14–80) 4F, 11M (6–60) 5F, 5M (26–58)	qRT-PCR ELISA/ serum	miR-1165-3p	Serum miRNA-1165-3p levels were significantly elevated in asthmatics vs controls and also significantly elevated in patients with AR or ABPA	serum miR-1165-3p can potentially be utilized as a noninvasive biomarker that is able to aid in the diagnosis and characterization of allergic asthma.
Mao et al., 2018 S29	CARAS AR	3 3	1F, 2M (37,20,18) 2F,1M (16,30,35)	RNA sequencing Bioinformatics analysis	miR-93–5p, miR-92a-3p and miR21–5p	SLC14A1, SNCA, TNS1, KAT2B and PARP1 were regulated by hsa-miR-93– 5p, hsa-miR-92a-3p and hsa-miR21–5p	These genes ad miRNA found may play an important role in the development of CARAS

1 st author, year REF	Disease	N	Gender (Age, yr)	Methods cells/tissues	microRNAs	Outcomes	Conclusions
Hu et al., 2017 82	AR,	176	92F, 84M 6.20 (1–12)	DNA genotyping qRT-PCR/ PBMc	miR-149	SNP rs2292832 in miR-149 was potentially associated with AR and AR + Asthma and AR patients with CC genotype and C allele of rs2292832 may have an increased asthma risk.	miR149 rs2292832 SNP may aggravate the susceptibility to AR and AR + Asthma through the modulation of mature miR-149 expression, which can be affected both by genetic and environmental factors
	AR + asthma	124	59F, 65M 7.11 (1–12)				
Geng et al., 2016 86	AR ± asthma	47	23F, 24M (29.5)	SPT, qRT-PCR ChIP, RNAi/ PBMc	miR-1792	miR-19a levels were significantly higher in peripheral B cells from AR patients as than in B cells from controls. Exposure of B cells from AR patients to specific allergen increased the levels if miR-19a and suppressed the expression of IL-10 in B cells	miR-19a plays an important role in mediating the effects of allergen-specific response in the suppression of IL-10 in B cells. miR-19a may be a novel therapeutic target for the treatment of allergic diseases
Yu et al., 2017 85	AR ± asthma	80	40F, 40M (34.6)	qRT-PCR WB ELISA ChIP assay RNAi/ serum and isolated peripheral B cells	miR-17-92 cluster	Treatment with either SIT or VD3 reduce serum levels of specific IgE and Th2 cytokines, suppresses miR-19a (one of the members of the miR-17-92 cluster) and increased IL-10 in peripheral B cells	Administration with VD3 promotes the effect of SIT on suppression of AR via repressing the expression of miR-19a in peripheral B cells.

ABPA: Allergic bronchopulmonary aspergillosis; AR: Allergic rhinitis; BPIFA1: BPI Fold Containing Family A Member 1; CARAS: Combined allergic rhinitis and asthma syndrome; CCL26: C-C Motif Chemokine Ligand 26; ChIP: Chromatin immunoprecipitation; CPA3: Carboxypeptidase A3; CST1: Cystatin SN; CT: Control; DEGs: Differentially-expressed genes; F: Female; Foxp3: Forkhead box P3; IgE: Immunoglobuline E; IL: Interleukin; KAT2B: K acetyltransferase 2B; M: Male; NAR: Non-Allergic Rhinitis; NECs: Nasal epithelial cells; Nno: Nasal Nitric Oxide; PARP1: Poly [ADP-ribose] polymerase 1; PBMc: Peripheral blood mononuclear cells; qRT-PCR: Quantitative Real-Time Polymerase Chain Reaction; RNAi: RNA interference; SCIT: Subcutaneous immunotherapy; SIT: Specific Immunotherapy; SLC14A1: Solute Carrier Family 14 Member 1; SLIT: Sublingual Immunotherapy; SNCA: Synuclein Alpha; SNP: Single nucleotide polymorphism; SPT: Skin Prick Test; Th2: T Helper 2; TNS1: Tensin 1; VD3: Vitamin D3; WB: Western Blotting.

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